Nonreciprocal Hopfield nets for the endothelial-mesenchymal transition: beyond the Waddington landscape

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Theories of cell differentiation are often framed in terms of a Waddington landscape, which implicitly assumes dynamics governed by a potential gradient. Here, we investigate endothelial cell differentiation during angiogenesis using single-cell RNA sequencing data combined with RNA velocity inference. We cluster the data into three phenotypes (phalanx, stalk, and tip), extract transition fluxes, and construct an effective coarse-grained dynamics. From this, we estimate entropy production and apply a recent variational decomposition scheme to separate conservative (gradient) and nonconservative contributions. We find a nonzero nonconservative component, indicating cyclic probability currents and a breakdown of purely potential-driven dynamics.

Motivated by this, we introduce a generalized nonreciprocal Hopfield model in which the three endothelial phenotypes are encoded as stored patterns of an effective spin system. A dynamical mean-field description yields equations for the overlaps between phenotypes and system state. RNA-velocity-inferred drifts are used to constrain the nonreciprocal coupling matrix, yielding a data-informed nonequilibrium model of the endothelial-mesenchymal transition. Our results provide a quantitative nonequilibrium characterization of angiogenesis, reveal limitations of equilibrium landscape descriptions, and motivate nonreciprocal modeling frameworks for cell differentiation.